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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/461,652	06/05/95	KWON	B IND4-D11

18N2/0203

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EXAMINER	
KAUFMAN, C	
ART UNIT	**PAPER NUMBER**
1812	7

DATE MAILED: 02/03/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 11/22/96.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 5, 6, 21, 22, 24-26, & 19-20 is/are pending in the application.

Of the above, claim(s) 19-20 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 5, 6, 21, 22, 24-26 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

* U.S. GPO: 1996-410-238

DETAILED ACTION

1. The amendment filed on 11/22/96, paper # 6, has been entered.

Drawing

2. Figure 1 of the instant application is presented on two separate sheets. 37 C.F.R. § 1.84 (u)(1) states that when partial views of a drawing which are intended to form one complete view, whether contained on one or several sheets, must be identified by the same number followed by a capital letter. The two sheets of drawing which are labeled "Figure 1" in the instant specification should be renumbered "Figure 1A and 1B". Applicant is reminded that once the drawings are changed to meet the separate numbering requirement of 37 C.F.R. § 1.84 (u)(1), Applicant is required to file an amendment under 37 C.F.R. § 1.312 to change the Brief Description of the Drawings and the rest of the specification accordingly. If, for example, Figure 1 is divided into Figures 1A and 1B then the Brief Description and all references to this figure in the specification must refer to Figures 1A and 1B.

Sequences Presented in Drawing Figures

3. 37 CFR 1.821(b) requires exclusive conformance, with regard to the manner in which the nucleotide and / or amino acid sequences are presented and described, with the sequence rules for all applications that include nucleotide and amino acid sequences that fall within the definitions. When a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the sequence identifier ("SEQ ID NO:X") must be used, either, in the drawing or in the Brief Description of the Drawings. (See MPEP 2422.02.) Figure 1 of the current application, which represents the 4-1BB sequence must be accompanied by a sequence identifier and be included in the Sequence Listing and CRF.

Specification

4. The disclosure is objected to because of the following informalities: On page 7, line 12, an amendment filed 11/22/96 added the words --also shown in SEQ ID NO: 1 and SEQ ID NO: 2-- after "4-1BB"; however, according to the description in the Sequence Listing, SEQ ID NO: 1 and 2 represent H4-1BB and not the mouse homologue; p. 6, line 18, "legand" should be --ligand--; p. 9, line 6, "inonoclonal" is not an art recognized word; p. 13, line 26, "inununoglobulin" should be --immunoglobulin--; p. 14, line 14, "CD4-0" should be --CD40--; p. 14, line 22, a repetition occurs in the form of "one 1" and should be eliminated; p. 15, line 6, "degenerative" should be --degenerate--, p. 16, line 2, "sequence id. 1" should be --SEQ ID NO: 1--; and p. 17, line 37, "ligan" should be --ligand--.

Appropriate correction is required.

Election/Restriction

5. Applicant's election with traverse of Group I in Paper No. 6 is acknowledged. The traversal is on the ground(s) that the inventions are not distinct and searching Groups I and II would not constitute a serious burden on the examiner. This is not found persuasive because as stated in the original restriction requirement, the invention of Group I is a product and that of Group II is a method of producing that product. In addition to the distinct subjects of product and process, the product may be produced by another distinct process such as chemical synthesis. The claims of Group I require an extensive search in the protein and pharmaceutical fields. These claims also require consideration of therapeutic uses of proteins. On the other hand, the claims of Group II require an extensive search in the molecular biology and nucleic acid fields, with considerations relating to genetic code degeneration and nucleic acid use, for example. The searches and examinations of the two groups are not coextensive and it is held that conducting a search and examination of both groups would be a serious burden.

The requirement is still deemed proper and is therefore made FINAL.

6. Pending claims 5, 6, 21, 22, and 24-26 are under consideration.

Claims 19 and 20 remain withdrawn from consideration.

Response to Amendment

7. The objection of claims 6 and 22-24 of the specification for not complying with 37 CFR 1.821 is withdrawn in view of the amendment.

The rejection of claims 7 and 23 under 35 USC 112, first paragraph, are moot due to cancellation of the claims.

The rejection of claims 20, 25, and 26 under 35 USC 112, second paragraph, is withdrawn in view of the amendment and of the fact that claim 20 is not under consideration.

The rejection of claim 7 under 35 USC 112, fourth paragraph, is withdrawn in view of the cancellation of claim 7.

Applicant's arguments filed 11/22/96 have been fully considered but they are not persuasive.

8. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 101

9. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claim 6 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Since the claimed protein is naturally occurring on human lymphocytes (see p. 15, last two paragraphs) and is not claimed as purified and/or isolated, the claims do not

show the hand of man involved in the invention and, therefore, are unpatentable. See MPEP § 706.03(a) and 2105.

Claim Rejections - 35 USC § 112, first paragraph

10. The rejection of claims 21, 24, and 25-26 under 35 U.S.C. 112, first paragraph, are maintained for the reason of record in paragraphs 4b, 4d, and 4e, respectively, in the previous Office action filed 4/19/96 (paper no. 4). For the rejection of claims 25 and 26 put forth in paper no. 4, deletion of the term "an effective amount" by the amendment filed 11/22/96 obviates only the related part of the rejection of record.

It is noted in the response to the rejection of claims 21 and 24 under 35 U.S.C. 112, first paragraph, that the response holds that the claims should be interpreted to only include proteins that have the biological activity of H4-1BB. However, the claims recite no function or other defining characteristic of human 4-1BB or H4-1BB aside from (as amended) specific amino acids of SEQ ID NO:2. The claims refer to the polypeptide by name and the specification does not define H4-1BB by function. If it is shown that 4-1BB or a homologous receptor from another non-human species binds a H4-1BB ligand, for example, then--according to the arguments presented in paper no.4--that other receptor is encompassed by the current claims because it has a biological activity of H4-1BB. Such receptors are outside the scope of the current invention. Also, the specification does not provide an enabling description of the extracellular domain of H4-1BB or of the H4-1BB ligand. The biological activity of H4-1BB is not described to the extent that one skilled in the art could make the invention based on activity and would not know how to use the fragments claimed.

NEW REJECTIONS:

11. Claim 5 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the full-length receptor having SEQ ID NO: 2, does not reasonably provide

enablement for another receptor/polypeptide produced from cDNAs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claim identifies H4-1BB only by name, without any other distinguishing characteristics. On page 4, lines 29-34, of the specification it is stated that H4-1BB can be produced by transfection of the cDNA of H4-1BB in a host cell. The name "H4-1BB" could encompass undisclosed fragments, deletions, polymorphisms, or mutations of its protein or cDNA, which are not supported by the specification. The specification does not teach how to make these molecules. Additionally, it encompasses non-functional H4-1BB receptor proteins that, for example, fail to bind a ligand or to elicit a response to ligand binding, which the specification has not taught how to use. Molecules, such as the ones mentioned above, that are embraced by the claims are not adequately described by the specification and it would require undue experimentation to make and use a number of proteins or cDNAs that are representative of the great quantity of molecules encompassed by the claim. Because at the time the invention was made, neither the ligand, the signal response pathway, nor a direct physiological response had been identified, structural information is critical to the practice of the invention.

12. Claim 21 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the full-length protein of SEQ ID NO:2, does not reasonably provide enablement for fragments of that protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In claim 21, the protein, because it is referred to by name and not SEQ ID NO, may contain only 12 amino acids. As pointed out in the previous Office action, the specification does not say what this peptide can be used for or what its functional properties are. The peptide is not part of the proposed signal sequence as described for 4-1BB in Fig. 1 (p. 7, line 19). The prior

art teaches only mouse 4-1BB and the prior art and specification do not describe in any detail which amino acids are required for a function specific to 4-1BB. Also 4-1BB and H4-1BB have only a 65% sequence identity at the amino acid level. No function or characteristics of the polypeptide of claim 21 are recited. Further, in reference to a polypeptide that comprises the recited N-terminal peptide, one skilled in the art would not be able to predict which amino acids aside from the twelve are necessary for, for example, ligand binding or B cell proliferation. In view of the lack of information pertaining to critical amino acids in H4-1BB, the identification of the claimed polypeptide by name only, and the use of the open language "comprising" in the claim, making and using a representative number of polypeptides encompassed by the breadth of claim would require undue experimentation.

13. Claims 22 and 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide having the full-length sequence of SEQ ID NO:2, does not reasonably provide enablement for fragments thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification does not disclose any characteristics of the H4-1BB aside from the full length cDNA sequence which encodes it and its deduced amino acid sequence. There is no information about the amino acids which comprise a signal sequence, transmembrane domains, a ligand binding domain, or a signal transduction domain. In the specification (p. 11, lines 16-17, and p. 17, lines 23-24, respectively) it is suggested that 4-1BB may represent a cell-surface molecule involved in T-cell-APC interaction and may be involved in T-cell activation. No defined role for 4-1BB had been established at the time the current application was filed. Also, the prior art teaches only mouse 4-1BB, and 4-1BB and H4-1BB have only about 65% cDNA sequence similarity (p. 4, lines 23-24) and differ in length by one amino acid. While the specification does disclose a putative signal peptide from amino acids 1-23 of 4-1BB (Fig. 1), no signal sequence is

identified for H4-1BB and there is extremely low sequence similarity between amino acids 1-23 of 4-1BB and H4-1BB (see Fig. 1 compared to SEQ ID NO: 2). One skilled in the art would not reasonably expect amino acids 1-23 of H4-1BB to comprise a signal peptide based on the information in the prior art and current specification; therefore, the functional properties of a fragment of H4-1BB beginning at amino acid 24 would be unpredictable. Additionally there is no basis in the specification for a H4-1BB (or 4-1BB) protein that ends at amino acid 186 of SEQ ID NO: 2. In view of the lack of information pertaining to amino acid positions and to domains of H4-1BB, and of the dissimilarity in sequence between H4-1BB and 4-1BB, it would require undue experimentation to use the claimed polypeptides.

14. Claims 25 and 26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

No guidance or examples pertaining to the use of a H4-1BB polypeptide have been disclosed that would provide a reasonable expectation of success when using the claimed invention to treat a disease or clinical condition. The specification says merely that H4-1BB is expected to act like 4-1BB, which "helped B cells with proliferation" (p. 17, lines 1-4). Further, the use of H4-1BB is unpredictable because, as the specification says on p. 17, lines 4-5, the derivative H4-1BB-AP can be used to suppress or enhance human immune responses. No guidance or examples are given to enable one skilled in the art to use the claimed protein to ameliorate a condition by, for example, suppressing an immune response. Nor is it disclosed how to select enhancing *versus* suppressing activity. On page 18, lines 6-7, it is stated that H4-1BB-AP can be used for the treatment of certain autoimmune diseases. Specific diseases are not listed and it would require undue experimentation to determine which autoimmune diseases could be treated with H4-1BB or its derivative. For these reasons and because no dosage or information on toxicity, stability, half-life, or solubility of H4-1BB or fragments or derivatives thereof was

available at the time the invention was made, it would require undue experimentation to use the claimed invention.

Claim Rejections - 35 USC § 112, second paragraph

15. Claims 21, 22, and 24-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 21, 22, and 24-26 are indefinite because the use of "human 4-1BB" is confusing since the specification defines "H4-1BB" as the human receptor homologous to the mouse receptor, which is defined as "4-1BB" (p. 1, lines 25-26, and p. 14, lines 26-27).

Claim 21 is indefinite because it is unclear what the composition of the claimed polypeptide is, whether it is only the amino acids listed or also includes undisclosed subject matter.

Priority

16. The effective filing date of the instant claims is deemed to be 9/16/93, the filing date of parent application 08/122,796, because the earlier filed parent applications do not disclose, under the test of 35 U.S.C. 112, first paragraph, the instantly claimed H4-1BB.

Only application 08/122,796 to which priority of the current application is claimed satisfies the enablement and description requirements of 35 U.S.C. 112, first paragraph, for the human receptor protein H4-1BB. Further, in applications 08/012, 269, of which application 08/122,796 is a CIP, only the mouse 4-1BB is described. While the specification of 08/012, 269 does say that identifying a human homology of 4-1BB is possible using probes from 4-1BB, neither the sequence of H4-1BB nor characteristics specific enough to allow it to be distinguished over other receptors in the art are disclosed. It does not appear that the inventors were in possession of the

claimed invention at the time application 08/012, 269 was filed, and one skilled in the art would not have been able to make the claimed invention without undue experimentation.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5, 6, 21, 22, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwarz et al. (U: GenBank CD-ROM release) in view of Ayala et al (V).

Schwarz et al. teach the polynucleotide sequence and deduced amino acid sequence of a receptor that is a member of the human nerve growth factor/tumor necrosis factor receptor family and which induces lymphocyte activation (hence called "ILA" by the authors). Schwarz et al. do not teach the purified encoded protein or a recombinant method of producing the protein.

The nucleotide of the prior art encodes a receptor which is 99.8% identical at the amino acid level to the claimed receptor, with a single conservative amino acid exchange at amino acid position 107 (K ->R, see attached "Sequence Comparison"). Like the receptor taught by Schwarz et al., the claimed receptor is "structurally related to member of the nerve growth factor receptor super-family," (p. 8, lines 29-30) and induces lymphocyte activation by interacting with B and T cells (abstract, lines 13-25).

Ayala et al. teach (p. 45, 1st full paragraph) that "many, and possibly all, genes have multiple alleles, i.e., they exist in more than two allelic forms, though any one diploid organism can carry no more than two alleles." Ayala et al. do not teach H4-1BB.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the nucleic acid taught by Schwarz et al. to produce and use the encoded protein

with a K107R conservative amino acid exchange of two basic amino acids because it would have been obvious to make any conservative change with the reasonable expectation that function and three-dimensional structure would have been maintained from such a *de minimus* change. Alternatively, it would have been obvious to obtain allelic variants of the protein encoded by the nucleic acid taught by Schwarz et al. because, as taught by Ayala et al, most genes have alleles. The protein of the current application is an allele of Schwarz et al. and, therefore, is an obvious variant over the prior art. One would have reasonably expected the claimed and published protein to be identical in function and other physical characteristics. The method of using a nucleic acid to recombinantly produce a protein is old and well known in the art. It would have been a routine step by one skilled in the art to subclone the nucleic and produce the protein to determine its characteristics (*e.g.*, ligand binding, length, structure). One would have been motivated to determine such characteristics knowing that the encoding nucleic acid had homology to nerve growth factor/tumor necrosis factor receptor because such factors were know in the art to affect clinically relevant cell growth and function. Note that claims 21, 22, and 24 use the open language "comprises", so that the polypeptides claimed read on the full-length polypeptide taught by Schwarz et al. Also, claim 5 is to the receptor protein which is the same protein regardless of whether it is made recombinantly, synthesized, or produced naturally.

In the applicant's submission of Schwarz et al. (paper 5, 5/6/96), a statement by the applicant asserts that the submitted sequence with accession number L12964 was not available to the public until Schwarz et al. published their paper (DA). This is incorrect. The letter by Genome Sequence DataBase Support Staffer, John O'Neill, which heads the copy of the sequence listing submitted in paper 5 (5/6/96) says that L12964 was released in June, 1993, in the GenBank CD-ROM. After contacting the National Center for Biological Informatics (NCBI) on 1/21/97, it was confirmed by the Examiner that indeed the sequence was available to the public on June 12, 1993, coincident with the release of the CD-ROM in June of that year. The e-mail that heads the

sequence data for ILA does not say the sequence was unavailable to the public. Generally, CD-ROMs containing sequence data are released for the purpose of publicly disseminating the sequence information contained therein.

Conclusion

17. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Friday from 8:00AM to 4:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Stephen Walsh, can be reached at (703) 308-2957.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

The Art Unit 1812 Fax Center number is (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

cmk
January 23, 1997

Stephen Walsh
STEPHEN WALSH
SUPERVISORY PATENT EXAMINER
GROUP 1800